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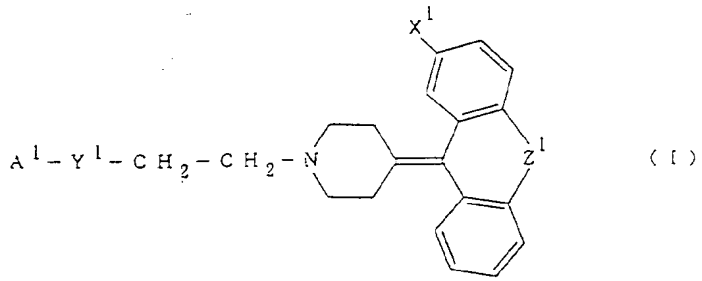
(54) Piperidine derivates and anti-platelet agents containing the same.

(57) Piperidine derivatives of general formula (I) or pharmaceutically acceptable salts thereof are useful in the manufacture of a medicament for use as a serotonin antagonist :



(I)

wherein A^1 represents an unsubstituted or substituted pyridyl, piperidyl, piperidino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino or piperazinyl group, a substituted alkyl group having

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from 1 to 8 carbon atoms, a substituted cycloalkyl group having from 4 to 8 carbon atoms, or an unsubstituted or substituted alkoxyl group having 1 to 8 carbon atoms,
X^1 represents a hydrogen atom or a halogen atom,
Y^1 represents one of the organic groups :
-CONH-, -NHCO-, -$CONHCH_2$-, -$(CH_2)_n$-, -COO-,
wherein n is an integer of from 0 to 4, and
Z^1 represents one of the organic groups :
-CH=CH-, -S-CH_2-, -S-, -CH_2-CH_2-.

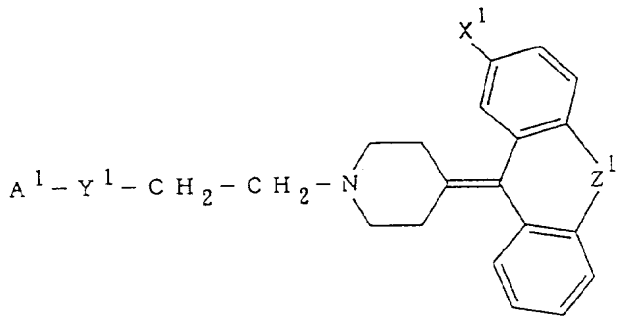
The present invention relates to a novel serotonin antagonist and an anti-platelet agent, more particularly, a serotonin antagonist and an anti-platelet agent which potently and specifically inhibit the serotonin 2 receptor with low adverse side effect.

It is considered that the thrombus greatly participates in ischemic disorders such as cardiac infarction and cerebral infarction and, in particular, the platelet plays an important role in the formation of the arterial thrombus. Known anti-platelet agents include arachidonic acid metabolism-inhibiting agents, platelet cyclic nucleoside-related agents, thromboxane receptor antagonists, and aspirin and ticlopidine have been clinically used. However, their effect is not sufficient and thus development of more effective agents has been in demand.

On the other hand, it is known that serotonin (5HT), which is stored in α granules of the platelet, is released by activation of the platelet caused by various stimulations, and the released serotonin increases the calcium ion level in the cell via the serotonin 2 ($5HT_2$) receptor on the platelet membranae, resulting in aggregation of the platelet. It is also considered that the $5HT_2$ receptor existing in the vascular smooth muscle participates in the blood vessel contraction. Accordingly, the $5HT_2$ receptor antagonist is expected to have vasoconstriction inhibiting activity in addition to the platelet aggregation inhibiting activity and, therefore, there is a possibility that a potent anti-thrombus function is obtained with the $5HT_2$ receptor antagonist.

The object of the present invention is to provide a serotonin antagonist and an anti-platelet agent which potently and specifically inhibit the serotonin 2 receptor with low adverse side effect.

The present invention relates to a serotonin antagonist or an anti-platelet agent which comprises as an active ingredient a piperidine derivative represented by the following general formula (I):



(I)

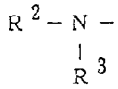
wherein A^1 represents an unsubstituted or substituted pyridyl, piperidyl, piperidino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino or piperazinyl group, a substituted alkyl group having from 1 to 8 carbon atoms, a substituted cycloalkyl group having from 4 to 8 carbon atoms, or an unsubstituted or substituted alkoxyl group having 1 to 8 carbon atoms, X^1 represents a hydrogen atom or a halogen atom, Y^1 represents one of the following organic groups:

-CONH-, -NHCO-, $-CONHCH_2-$, $-(CH_2)_n-$, -COO-, wherein n is an integer of from 0 to 4, and Z^1 represents one of the following organic groups:

-CH=CH-, $-S-CH_2-$, -S-, $-CH_2-CH_2-$, or a salt thereof.

As the substituent for A^1 in the above general formula (I), the following groups are preferable.

R^1-CO-,



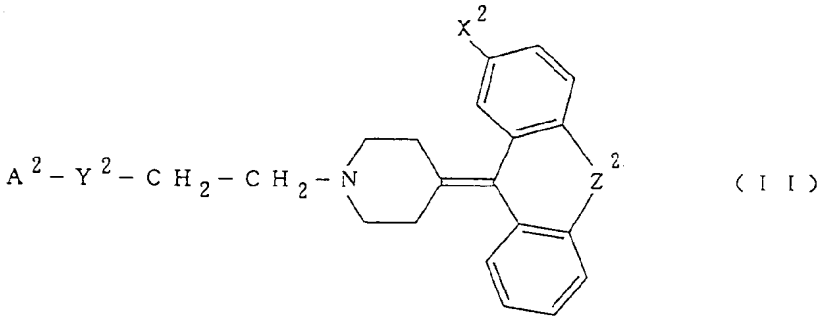
wherein R^1 is a hydrogen atom, an alkyl or alkoxyl group having from 1 to 6 carbon atoms, an amino group which may be substituted by an alkyl group, or an acylaminoalkyl group, and R^2 and R^3, which may be the same or different, each represents a hydrogen atom, an alkyl, acyl or alkoxycarbonyl group having from 1 to 6 carbon atoms, or an aminocarbonyl group which may be substituted by an alkyl group.

Illustrative examples of such substituents include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-formylglycyl, N-acetylglycyl, N-formylm-β-alanyl, N-acetyl-β-alanyl, N-methyl-N-formyl, N-methyl-N-acetyl, N-methyl-N-propionyl, N-ethyl-N-formyl, and N-ethyl-N-acetyl.

Preferable examples of Y^1 in the general formula (I) include a group -CONH-, and preferable examples of

Z^1 include -CH=CH-.

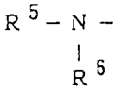
Among the compounds represented by the general formula (I), the compounds represented by the following general formula (II) are novel compounds that have not described in the references.



(II)

wherein A^2 represents an unsubstituted or substituted piperidyl, piperidino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino or piperazinyl group, a substituted alkyl group having from 1 to 8 carbon atoms, a substituted cycloalkyl group having from 4 to 8 carbon atoms, or an unsubstituted or substituted alkoxyl group having 1 to 8 carbon atoms. When A^2 has a substituent, the substituent is one of the following groups.

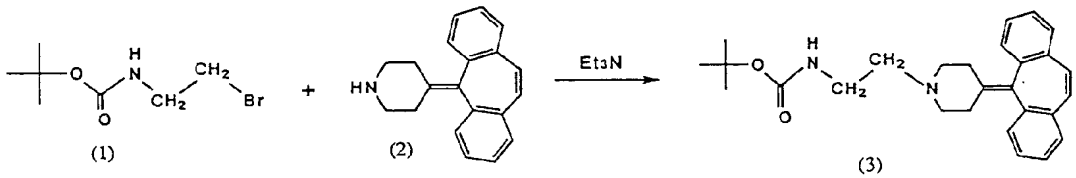
R^4-CO-,



wherein R^4 represents an alkyl or alkoxyl group having from 1 to 6 carbon atoms, an amino group which may be substituted by an alkyl group, or an acylaminoalkyl group, R5 and R^6, which may be the same or different, each represents a hydrogen atom, an alkyl, acyl or alkoxycarbonyl group having from 1 to 6 carbon atoms, or an aminocarbonyl group which may be substituted by an alkyl group, and X^2, Y^2, and Z^2 respectively have the same meanings with X^1, Y^1, and Z^1.

As the substituent for A^2, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-formylglycyl, N-acetylglycyl, N-formyl-β-alanyl, N-acetyl-β-alanyl, N-methyl-N-formyl, N-methyl-N-acetyl, N-methyl-N-propionyl, N-ethyl-N-formyl, N-ethyl-N-acetyl, and the like are preferable. As Y^2 and Z^2, a group -CONH- and a group -CH=CH- are respectively preferable.

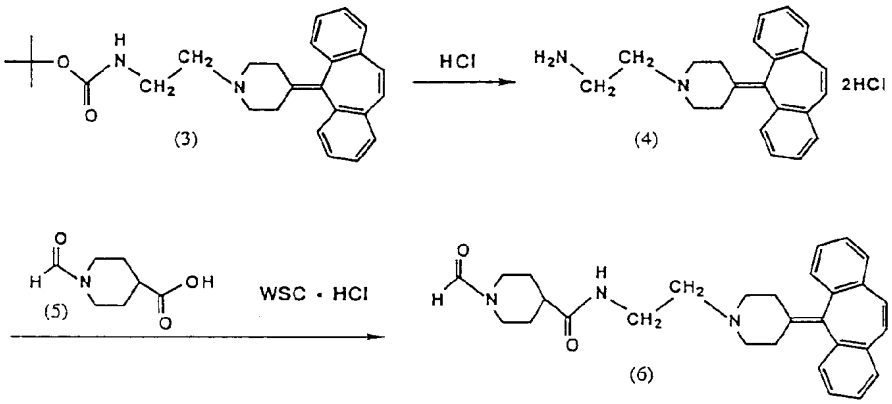
The piperidine derivative represented by the above general formula (I) may be prepared by the conventional method, for example, by the method described in an unexamined published Japanese patent application 3-47168. For example, 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-t-butoxycarbonylamino)ethyl)piperidine (compound (3)) included in the general formula (I) can be easily obtained by subjecting N-t-butoxycarbonyl-2-bromoethylamine (compound (1)) and 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (compound (2)) to the condensation reaction in the presence of a base such as triethylamine, as shown in the Reaction Scheme I.



(1) (2) (3)

Similarly, 1-formyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide (compound (6)) included in the general formula (I) can be easily obtained by subjecting the compound 4, which is obtained by removing a t-butoxycarbonyl group from the compound 3 using 4 M hydrochloric acid/dioxane, etc., and 1-formylisonipecotic acid (compound (5)) to the condensation reaction using a condensation agent

such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, as shown in the Reaction Scheme II.



The reaction product obtained by these production methods is isolated and purified as a free compound or a salt thereof. Isolation and purification may be carried out by extraction, concentration, evaporation, crystallization, and various types of chromatography.

Examples of the salt of the piperidine derivative include acid addition salts with inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid and with organic acids such as formic acid, acetic acid, lactic acid, salicylic acid, mandelic acid, citric acid, oxalic acid, maleic acid, fumaric acid, tartaric acid, tannic acid, malic acid, p-toluenesulfonic acid, methanesulfonic acid, and benzenesulfonic acid.

The piperidine derivative represented by the general formula (I) exhibits a serotonin antagonizing activity and is useful as an agent for the treatment of ischemic disorders, thrombosis, obstruction, mental diseases (depression, anxiety), diabetic complication, arteriosclerosis, hypertension, arrhythmia, migraine, microcirculation failure, and the like. In particular, as an anti-platelet agent, the piperidine derivative represented by the general formula (I) is useful as an agent for the treatment of various ischemic disorders, thrombosis, obstruction, angiitis, diabetic complication, arteriosclerosis, nephropathy, and ulcer, pain, rhigosis, etc. due to chronic arterial obstruction, and also can be used as a treating agent for improving various ischemia accompanying circulation failure, for preventing restenosis after surgical treatment of ischemic heart diseases, and for improving blood circulation.

When the piperidine derivative of the general formula (I) is used as a serotonin antagonist or an anti-platelet agent, the administration route may be either oral or parenteral. Though the clinical dose may differ depending on the age, body weight, and condition of the patient and on the administration method, but the dose per an adult per day is generally from 0.01mg to 500mg, preferably from 0.1mg to 50mg, in the case of oral administration and 1μg to 100mg, preferably from 0.01mg to 10mg, in the case of parenteral administration.

As the dosage form, usual dosage forms such as tablets, powders, sugar-coated preparations, capsules and solutions may be employed and such dosage forms can be prepared by the conventional method making use of usual pharmaceutical adjuvants.

Examples

Then, the present invention will be further illustrated by way of Examples but the present invention should not be construed as being limited thereto.

Preparation procedure A

Synthesis of 1-methoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclo ohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamidehydrochloride

Step 1

Synthesis of 2-t-Butoxycarbonylaminoethylbromide

2-Aminoethylbromide hydrobromide (35.77 g, 174.6 mmol) and di-t-butyl dicarbonate (22.80 g, 104.5

mmol) were added to a mixed solvent of 300 ml of diethyl ether and 300 ml of water. Then, sodium hydrogencarbonate (44.00 g, 523.7 mmol) was gradually added and the mixture was stirred at room temperature overnight. The diethyl ether layer was washed with 80 ml of 1N hydrochloric acid and then with 80 ml of a saturated aqueous sodium chloride solution, and dried over magnesium sulfate powder. The solvent was evaporated to obtain the titled compound.
Amount obtained: 21.57 g (96.25 mmol); Yield: 92%

Step 2

Synthesis of 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-t-butoxycarbonylamino)ethyl)piperidine

2-t-Butoxycarbonylaminoethylbromide (4.5 g, 20.1 mmol), 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (2.7 g, 10.0 mmol), and triethylamine (4.2 ml, 30 mmol) were added to acetonitrile (300 ml), and the mixture was stirred on an oil bath at 50°C for 16 hours. The temperature was lowered to room temperature, the solvent was evaporated, and the residue was dissolved in 300 ml of ethyl acetate. After removing insoluble matters by filtration, the filtrate was washed with 100 ml of 1N hydrochloric acid, 100 ml of a 1N aqueous sodium hydroxide solution, and 100 ml of a saturated sodium chloride aqueous solution, and dried over magnesium sulfate powder. The solvent was evaporated and the residue was purified by silica gel column chromatography to obtain the titled compound.
Amount obtained: 3.6 g (8.6 mmol); Yield: 86%

Step 3

Synthesis of 1-(2-aminoethyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine dihydrochloride

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-t-butoxycarbonylamino)ethyl)piperidine (8.47 g, 20.4 mmol) was dissolved in 100 ml of dichloromethane, and 100 ml of a 4N hydrochloric acid-dioxane solution was added thereto, followed by stirring at room temperature for 1 hour. The solvent was evaporated to obtain the titled compound (8.56 g).

Step 4

Synthesis of 1-t-butoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide

1-(2-Aminoethyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine dihydrochloride (2.3 g, 6.0 mmol), 1-t-butoxycarbonylisonipecotic acid (1.6 g, 7.2 mmol), triethylamine (3.0 ml, 21.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.4 g, 7.2 mmol) were mixed, and the mixture was stirred at room temperature overnight. After evaporating the solvent, the residue was dissolved in 100 ml of dichloromethane, washed with 100 ml of 1N hydrochloric acid, 100 ml of a 1N aqueous sodium hydroxide solution, and 50 ml of a saturated aqueous sodium chloride solution. The solvent was evaporated and the residue was purified by silica gel chromatography to obtain the titled compound.
Amount obtained: 2.0 g (3.8 mmol); Yield: 63%

Step 5

Synthesis of N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide dihydrochloride

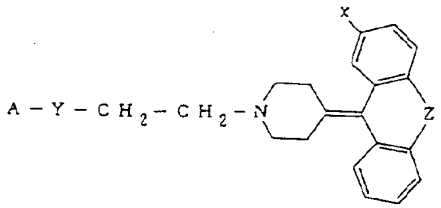
10 ml of 4N hydrochloric acid-dioxane solution was added to 1-t-butoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide (0.10 g, 0.185 mmol), and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated to obtain the titled compound.
Amount obtained: 0.093 g (0.186 mmol); Yield: 100%

Step 6

Synthesis of 1-methoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide hydrochloride

N-(2-(4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide dihydrochloride (0.59 g, 1.18 mmol) and triethylamine (0.8 ml, 5.70 mmol) were dissolved in 50 ml of dichloromethane, and methyl chloroformate (0.1 ml, 1.40 mmol) was added. The mixture was stirred for 1 hour and 100 ml of dichloromethane was added. The mixture was washed with 70 ml of water, 70 ml of a 1N aqueous sodium hydroxide solution, and 70 ml of a saturated aqueous sodium chloride solution, and purified by silica gel chromatography. The product obtained was converted into the hydrochloride form to give the titled compound. Amount obtained: 0.39 g (0.75 mmol); Yield: 63%

The compounds shown in Table 1 were produced by the similar manner as described in Preparation procedure A.



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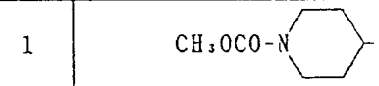
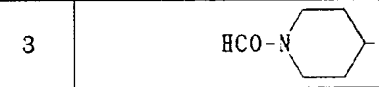
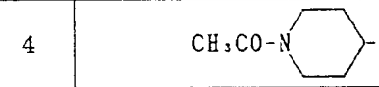
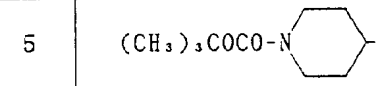
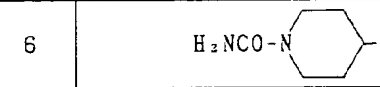
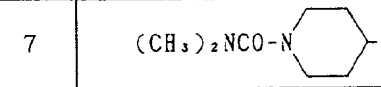
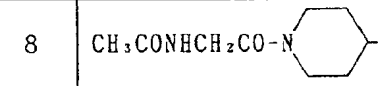
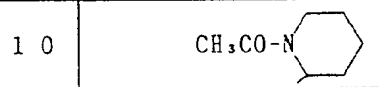
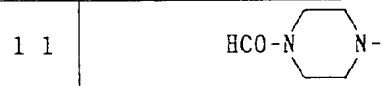
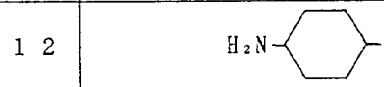
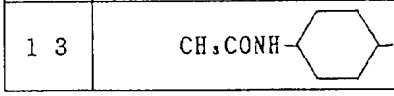
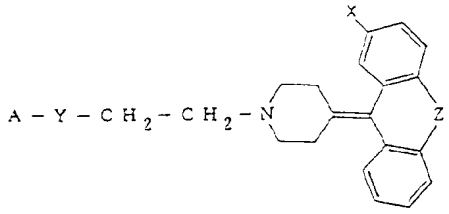
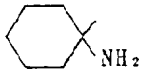
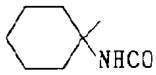
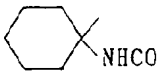
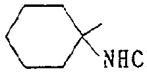
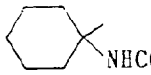
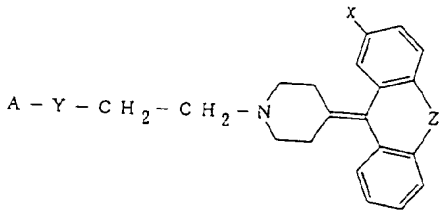
1		-CONH-	H	-CH=CH-	8.2	7.5
2					8.6	7.3
3					8.4	7.2
4					8.5	7.2
5					8.0	6.5
6					—	6.9
7					8.5	6.7
8					7.9	6.6
9					7.8	7.1
10					8.8	—
11					8.8	7.0
12					8.6	6.6
13					9.3	—



	A	Y	X	Z	pKi	pIC_{50}
14	$(CH_3)_3COCONH$- 	-CONH-	H	-CH=CH-	—	—
15					—	—
16	CH_3CH_2O-				—	7.6
17	$(CH_3)_3CO$-				—	7.0
18					8.9	7.3
19					8.3	6.4
20					8.0	6.3
21					7.8	6.5
22					8.2	5.8
23	$H_2N(CH_2)_3$-				—	7.6
24	$HCONH(CH2)_3$-				9.8	7.2
25	$CH_3CONH(CH_2)_3$-				9.2	6.6
26	$(CH_3)_3COCONH(CH_2)_3$-				—	7.2



	A	Y	X	Z	pKi	pIC_{50}
27	$(CH_3)_2NCONH(CH_2)_3$-	-CONH-	H	-CH=CH-	9.2	6.9
28	$CH_3NH(CH_2)_3$-				–	6.6
29	$(CH_3)_3COCON(CH_2)_3$- CH_3				–	7.1
30	HCO-N⟨⟩-	-$CONHCH_2$-			8.3	6.4
31	$(CH_3)_3CO$-				8.8	–
32	H_2N-	-CH_2-			–	–
33	HCO-N⟨⟩-	-COO-			8.3	7.4
34	H_2N-	–		-CH_2-CH_2-	–	–
35	$(CH_3)_3CO$-	-CONH-			8.3	–
36	HCO-N⟨⟩-				8.9	5.8
37	H_2N-	–		-S-	8.4	5.0
38	$(CH_3)_3CO$-	-CONH-			9.1	7.3
39	HCO-N⟨⟩-				9.2	7.1
40	HCO-N⟨⟩-		F	-S-CH_2-	7.1	5.6

Preparation procedure B

Synthesis of 1-(4-(4-(5H-dibenzo[a d]cyclohepten-5-ylidene)-1- piperidinyl)butyl)morpholine

Step 1

Synthesis of 1-(4-oxo-4-morpholinobutyryl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

In 50 ml of dichloromethane, 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (0.27 g, 1.0 mmol), succinic anhydride (0.12 g, 1.2 mmol), and triethylamine (0.17 ml, 1.2 mmol) were stirred at room temperature

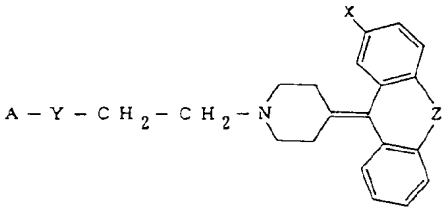
overnight. Morpholine (0.14 ml, 1.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) were added and the mixture was further stirred at room temperature for 8 hours. The reaction mixture was washed with 30 ml of 1N hydrochloric acid, 30 ml of a 1N aqueous sodium hydroxide solution, and 30 ml of a saturated aqueous sodium chloride solution, dried over magnesium sulfate powder, and purified by silica gel chromatography to obtain the titled compound.
Amount obtained: 0.44 g (1.0 mmol); Yield: 100%

Step 2

Synthesis of 1-(4-(4-(5H-dibenzo[a,d]cyclohepten-5- ylidene)-1-piperidinyl)butyl)morpholine dihydrochloride

In tetrahydrofuran (60 ml), 1-(4-oxo-4-morpholinobutyryl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (0.44 g, 1.00 mmol) was reacted with lithium aluminum hydride (0.38 g, 10.0 mol) at 0°C, and further treated in accordance with the conventional method to obtain the titled compound.
Amount obtained: 0.32 g (0.66 mmol); Yield: 66%

The compounds shown in Table 2 were produced by the similar manner as described in Preparation procedure B.



	A	Y	X	Z	pKi	pIC_{50}
4 1		$-(CH_2)_2-$	H	-CH=CH-	8.2	6.9
4 2					8.7	6.6
4 3		$-(CH_2)_3-$			7.3	–
4 4		$-(CH_2)_2-$		$-CH_2-CH_2-$	7.9	–
4 5				-S-	8.1	–

Test Example 1

The binding affinity to the serotonin 2 receptor was evaluated using a bovine cerebral cortex membrane sample. To 200 µl of a bovine membrane sample adjusted to 50 mg (wet weight) membrane/ml were added 200 µl of 3 nM [^{3}H]-ketanserin and 200 µl of a test compound solution prepared by dissolving a test compound in 1.7% ethanol, followed by mixing. The mixture was incubated at 25°C for 30 minutes and filtered with a glass filter. The radioactivity trapped on the filter was measured with a liquid scintillation counter. The non-specific binding was defined by 10^{-6} M LY53857. The concentration of the test compound which inhibits 50% of the specific binding of [^{3}H]-ketanserin (i.e., IC_{50} value) was obtained, and the Ki value was calculated in accordance with the following equation. The results are shown as the negative logarithm of the Ki value (i.e., pKi value).

$$Ki = \frac{I\,C_{50}}{1 + \frac{[L]}{K_d}}$$

In the equation, Ki indicates the dissociation constant and [L] indicates the concentration of [^{3}H]-ketanserin.

From the results in Tables 1 and 2, it is apparent that the piperidine derivative of the present invention exhibits strong binding affinity to the serotonin 2 receptor.

Test Example2

The anti-platelet effect due to the serotonin antagonistic activity was measured *in vitro* using the platelet of SD rats (body weight: about 300 to 400 g, male). Platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared from blood with 0.38% sodium citrate which was obtained from aorta abdominalis of a rat under diethyl ether anesthesia. The platelet concentration of PRP was adjusted to 5 x 10^8 platelets/ml by adding PPP. Then, the test compound dissolved in 0.4% aqueous ethanol was added, and the mixture was incubated at 37°C for 3 minutes. The platelet aggregation induced by addition of 0.5 μM or 0.8 μM adenosine diphosphate (ADP) + serotonin was measured as an increase in optical transmittance of PRP. The concentration of the test compound which inhibits 50% of the increase in platelet aggregation which is obtained with serotonin without a test compound was measured, and its negative logarithm (pIC_{50}) was calculated. The results are shown in the Table 1 and 2. From these results, it is apparent that the piperidine compound of the present invention potently inhibits the platelet aggregation by serotonin.

Test Example 3

The anti-platelet effect due to the serotonin antagonistic activity was measured *en vivo* using SD rats (body weight: about 210 to 330 g, male). The test compound was dissolved or suspended in arabic gum and orally administered to the rat in a dose shown in Table 3. Two hours after the administration of the test compound, the rat was anesthetized with diethyl ether and platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared from blood with 0.38% sodium citrate which was obtained from aorta abdominalis of the rat. The platelet concentration of PRP was adjusted to 5 x 10^8 platelets/ml by adding PPP. Then, the PRP was incubated at 37°C for 3 minutes, and platelet aggregation induced by addition of 0.7 μM adenosine diphosphate (ADP) + serotonin was measured as an increase in optical transmittance of PRP. The aggregation occurred by addition of ADP alone and the maximum aggregation ratio by the simultaneous addition of ADP and serotonin were measured with respect to each group, and increase in aggregation caused by serotonin was calculated. The increase in aggregation caused by serotonin in the arabic gum administered group was taken as 100%, and the effect of the test compound was judged using as an index the increase in aggregation caused by the serotonin in the test compound-administered group (n = 3). The results are shown in the Table 3.

Table 3

Test compound	Amount of administration (mg/kg)	Increase in aggregation by serotonin (%)
arabic gum	-	100
compound of No. 3	0.1	75.7
	0.3	57.3
	1	24.3
	3	27
	10	-2.7
compound of No. 9	0.3	57.3
compound of No. 17	0.3	50.7
compound of No. 18	0.3	94.9
compound of No. 38	0.3	82.4
compound of No. 39	0.3	54.5
compound of No. 41	0.3	91.5

From the results in the Table 3, it is apparent that the piperidine compound of the present invention potently inhibits the platelet aggregation by serotonin even in the case of oral administration.

Test Example 4

The serotonin antagonistic activity in the central nerve system was evaluated by measuring the inhibiting effect on head twitch of mouse induced by 5-hydroxytryptophan (5HTP). A test compound in an amount of 1, 3, 10, or 30 mg was respectively dissolved in 100 ml of water and, 90 minutes before 5HTP administration, the solution (10 ml/kg body weight) was orally administered to a ICR mouse (body wight: 27 to 32 g, male) fasted from the previous day. As a control, 5% arabic gum was used. Carbidopa (6 mg/kg) was subcutaneously administered and, after 15 minutes, 5HTP (180 mg/kg) was intraperitoneally administered. From the 15 minutes after 5HTP administration, the number of head twitches occurred within 2 minutes were counted. The concentration of the test compound which inhibits 50% of the number of head twitches in the 5% arabic gum administered group was obtained. The results are shown in the Table 4.

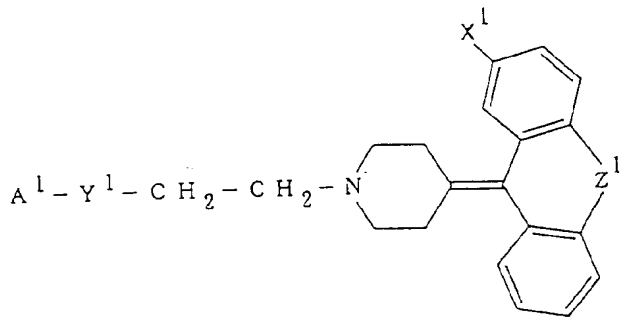
Table 4

Test compound	ID_{50}(mg/kg)
compound of No. 3	0.39
cycloheptadine	0.12

From the results in the Table 4, it is apparent that the piperidine compound of the present invention has low effect on the central nerve system and is a highly safe compound.

Claims

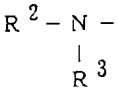
1. Use of a piperidine derivative of general formula (I) or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a serotonin antagonist:



(I)

wherein A^1 represents an unsubstituted or substituted pyridyl, piperidyl, piperidino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino or piperazinyl group, a substituted alkyl group having from 1 to 8 carbon atoms, a substituted cycloalkyl group having from 4 to 8 carbon atoms, or an unsubstituted or substituted alkoxyl group having 1 to 8 carbon atoms,
X^1 represents a hydrogen atom or a halogen atom,
Y^1 represents one of the organic groups:
-CONH-, -NHCO-, $-CONHCH_2-$, $-(CH_2)_n-$, -COO-,
wherein n is an integer of from 0 to 4, and
Z^1 represents one of the organic groups:
-CH=CH-, $-S-CH_2-$, -S-, $-CH_2-CH_2-$.

2. The use of claim 1, wherein A^1 has a substituent and said substituent is one of the groups:
R^1-CO-,



wherein R^1 is a hydrogen atom, an alkyl or alkoxyl group having from 1 to 6 carbon atoms, an amino group which may be substituted by an alkyl group, or an acylaminoalkyl group, and R^2 and R^3, which may be the same or different, each represents a hydrogen atom, an alkyl, acyl or alkoxycarbonyl group having from 1 to 6 carbon atoms, or an aminocarbonyl group which may be substituted by an alkyl group.

3. The use of claim 1 or claim 2, wherein the substituent is formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-formylglycyl, N-acetylglycyl, N-formyl-β-alanyl, N-acetyl-β-alanyl, N-methyl-N-formyl, N-methyl-N-acetyl, N-methyl-N-propionyl, N-ethyl-N-formyl or N-ethyl-N-acetyl.

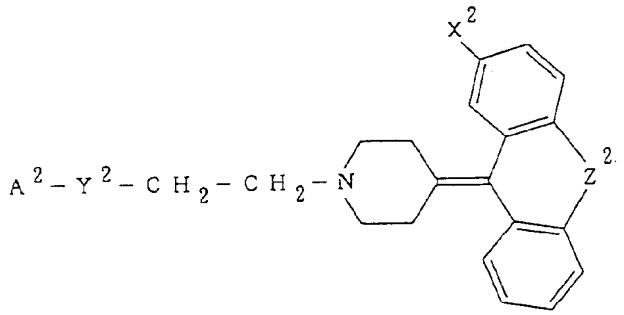
4. The use of any one of the preceding claims, wherein Y^1 is a group -CONH-.

5. The use of any one of the preceding claims, wherein Z^1 is a group -CH=CH-.

6. The use of any one of the preceding claims, wherein the piperidine derivative is 1-formyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide.

7. The use of any one of the preceding claims, wherein the medicament is an anti-platelet agent.

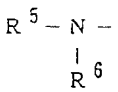
8. A piperidine derivative represented by the general formula (II):



(II)

wherein A^2 represents an unsubstituted or substituted piperidyl, piperidino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino or piperazinyl group, a substituted alkyl group having from 1 to 8 carbon atoms, a substituted cycloalkyl group having from 4 to 8 carbon atoms, or an unsubstituted or substituted alkoxyl group having 1 to 8 carbon atoms, when A has a substituent, said substituent is one of the groups:

R^4-CO-,



wherein R^4 represents an alkyl or alkoxyl group having from 1 to 6 carbon atoms, an amino group which may be substituted by an alkyl group, or an acylaminoalkyl group, R^5 and R^6, which may be the same or different, each represents a hydrogen atom, an alkyl, acyl or alkoxycarbonyl group having from 1 to 6 carbon atoms, or an aminocarbonyl group which may be substituted by an alkyl group, and
X^2, Y^2, and Z^2 respectively have the same meanings as X^1, Y^1, and Z^1 in claim 1,
or a salt thereof.

9. The piperidine derivative of claim 8, wherein A^2 has a substituent and said substituent is acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-formylglycyl, N-acetylglycyl, N-formyl-β-alanyl, N-acetyl-β-alanyl, N-methyl-N-formyl, N-methyl-N-acetyl, N-methyl-N-propionyl, N-ethyl-N-formyl or N-ethyl-N-acetyl, or a salt thereof.

10. The piperidine derivative of claim 8 or claim 9, wherein Y^2 is a group -CONH-.

11. The piperidine derivative of any one of claims 8 to 10, wherein Z^2 is a group -CH=CH-.

12. A compound selected from the group consisting of 1-methoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-carbamoyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-t-butoxycarbonyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-carbamoyl-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-(N,N-dimethylcarbamoyl)-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1- (N-acetylglycyl)-N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylpipecolamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-(N-acetyl)pipecolamide, 1-formyl-4-((2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylcarbamoyl)piperazine, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-aminocyclohexanecarboxamide, N-(2-(4-(5H- dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-acetylaminocyclohexanecarboxamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-(1-t-butoxycarbonylamino)cyclohexanecarboxamide, 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-ethoxycarbonylamino)ethyl)piperidine, 4-(5H-dibenzo[a,dicyclohepten-5-ylidene)-1-(2-t-butoxycarbonylamino)ethyl)piperidine, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-1-(1-amino)cyclohexanecarboxamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-1-(1-acetyla-

mino)cyclohexanecarboxamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-1-(1-t butoxycarbonylamino)cyclohexanecarboxamide, N-(2-(4-(5H-dibenzo [a,d] cyclohepten-5-ylidene)-1-piperidinyl))ethyl-1-(1-formylamino)cyclohexanecarboxamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-1-(1-N,N-dimethylcarbamoylamino)cyclohexanecarboxamide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-aminobutyramide, N-(2-(4-(5H-dibenzo[a,d]cy- clohepten-5-ylidene)-1-piperidinyl))ethyl-4-formylaminobutyramide, N-(2-(4-(5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-acetylaminobutyramide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-t-butoxycarbonylaminobutyramide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-(N,N-dimethylcarbamoylamino)butyramide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-(N-methylamino)butyramide, N-(2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl-4-(N-methyl-t-butoxycarbonylamino)butyramide, 1-formyl-N-(3-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))propylisonipecotamide, 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-t-butoxycarbonylaminopropyl)piperidine, 1-(3-aminopropyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine, 1-formyl-isonipecotic acid 2-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethyl ester, 1-(2-aminoethyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine, 4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-t-butoxycarbonylamino)ethyl)piperidine, 1-formyl-N-(2-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-(2-aminoethyl)-4-(9-thioxanthinidene)piperidine, 4-(9-thioxanthinidene)-1-((2-t-butoxycarbonylamino) ethyl)piperidine, 1-formyl-N-(2-(4-(9-thioxanthinidene)piperidinyl))ethylisonipecotamide, 1-formyl-N-(2-(4-(11H-dibenzo[b,e]thiepin-2-fluoro-11-ylidene)-1-piperidinyl))ethylisonipecotamide, 1-(4-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl)butyl)morpholine, 1-(4-(4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl)pentyl)morpholine, 1-(4-(4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl)butyl)piperidine, and 1-(4-(4-(9-thioxanthilidene)piperidinyl)butyl)morpholine.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 2647

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 307 303 (SYNTHELABO) * page 9; examples V,VI,VIII * ---	1,8	C07D211/70 C07D401/12 C07D409/04
A	EP-A-0 479 601 (AJINOMOTO CO., INC.) * e.g., compounds 3,74,75,89,94,95 * ---	1-12	C07D409/14 C07D413/06 C07D413/14
A D	EP-A-0 371 805 (AJINOMOTO CO., INC.) * e.g. examples 7,9-12,61-63,83,96-102 * & JP-A-03 047 168 (AJINOMOTO CO., INC.) ---	1-12	C07D417/06 A61K31/445
A	CHEMICAL ABSTRACTS, vol. 120, no. 21, 23 May 1994, Columbus, Ohio, US; abstract no. 270113w, * abstract * & JP-A-05 097 808 (AJINOMOTO KK.) 20 April 1993 ---	1-12	
A	EP-A-0 406 739 (HOKURIKU PHARMACEUTICAL CO., LTD.) * the whole document * ---	1-12	
A	FR-A-1 322 527 (SANDOZ S.A.) * the whole document * -----	1-12	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	18 September 1995	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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